

Organ Transplantation: A Practical Triumph and Epistemologic Collapse¹

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AT THE November 1970 meeting of the American Philosophical Society, Jonathan Rhoads organized and chaired a session on transplantation that consisted of five formal papers (1–5). By the time of this meeting, kidney, liver, heart, and pancreas transplantation already had been accomplished in humans and the first successful bone marrow transplantations had been recorded (Table 1) (6–10). But the results with these procedures were not yet good enough to generate much enthusiasm.

Moreover, it was not clear how to make things better. One reason was that workers in the burgeoning special field of transplantation immunology already had been disoriented by a conceptual error. As early as 1962, the mistaken conclusion had been reached “by consensus” that the engraftment of organs involved mechanisms fundamentally different from those of successful bone marrow transplantation. Although the error was a seemingly innocuous one, it became the basis of a false paradigm that precluded the orderly development of transplantation immunology, and limited progress in clinical transplantation almost exclusively to the development of more potent antirejection drugs.

THE SEED PLANTED BY MEDAWAR

How the invalid premise took root can be best understood from a historical perspective. The chain of events began during the Battle of Britain, when Peter Medawar, a twenty-four-year-old Oxford zoologist, was assigned to duty with the Scottish plastic surgeon Thomas Gibson. The objective of the two men was to determine if skin removed from recently dead persons could be used to surgically replace the burned skin of fire bomb victims.

¹ Read 25 April 2003, as part of a symposium in honor of Jonathan E. Rhoads.

TABLE 1. Historical firsts: patient and allograft survival exceeding one year

<i>Organ</i>	<i>Ref</i>	<i>City</i>	<i>Date of TX</i>	<i>Physician/Surgeon</i>
Kidney	6	Boston	1/24/59	Murray
Liver	7	Denver	7/23/67	Starzl
Heart	8	Cape Town	1/2/68	Barnard
Bone marrow	9	Minneapolis	8/24/68	Good
Pancreas*	10	Minneapolis	6/3/69	Lillehei

* Simultaneous kidney and pancreas allografts in patient who had diabetes-associated renal failure.
TX = transplantation.

Their studies provided evidence that rejection of the skin is an immune reaction (11, 12). The key observation came from experiments in which skin was repetitively transplanted from a specific donor to a given recipient, placing each graft after the preceding one had been rejected. The survival time of the skin was progressively shortened. For example, the time to rejection might be ten days for a first graft, five days for the next one, and only a few hours after four or five preceding grafts (Fig. 1).

This kind of immunity (subsequently termed adaptive immunity) resembles that mounted in response to infections such as tuberculosis, in which the invading microorganism can exist within host cells without killing them. It was later learned that adaptive immunity is dependent on white cells (leukocytes) that are generated in the bone marrow, and migrate through the blood to multiple destinations. The principal

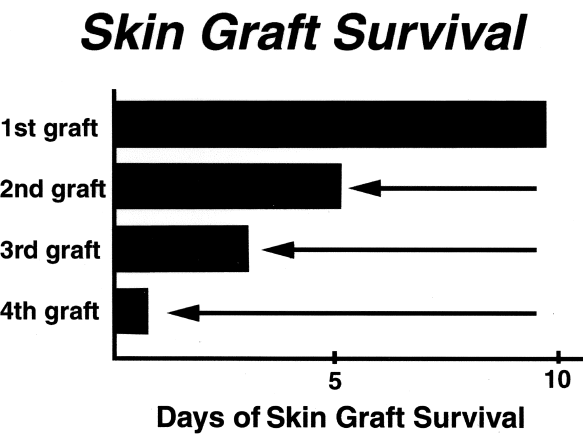


FIGURE 1. Peter Medawar’s experiment showing that when skin from the same donor is repetitively transplanted to a given recipient, graft survival becomes progressively shorter. This was convincing evidence that graft rejection is an immune response.

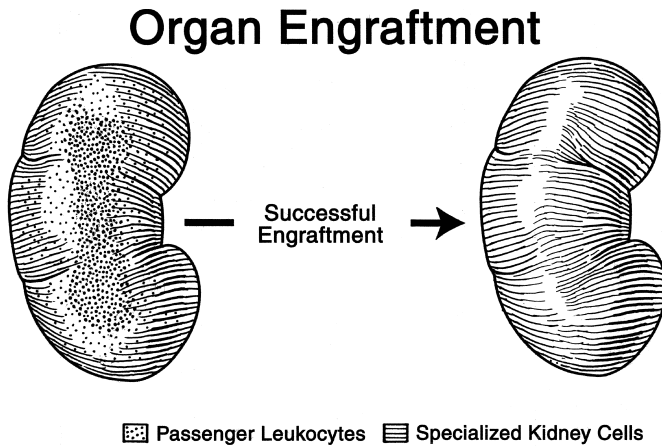


FIGURE 2. Part of the structure of all tissues and organs consists of white cells of bone marrow origin that are often referred to as passenger leukocytes. Left: these leukocytes are symbolized by a bone silhouette within a kidney. Right: after transplantation, these donor leukocytes disappear from a successfully engrafted organ and are replaced by similar recipient white cells.

leukocyte reservoirs are the bone marrow, spleen, and lymph nodes (and in lower mammals, the thymus gland). However, significant numbers of white cells of bone marrow origin also are part of the structure of all tissues and organs. These cells, often referred to as “passenger leukocytes,” are depicted symbolically in Figure 2 (left) by a bone silhouette within a kidney.

Very little of the foregoing information was known in the 1940s. In fact, it was not demonstrated until the late 1950s that the key leukocyte of the adaptive immune response is a white cell known as a lymphocyte. Nevertheless, Medawar’s demonstration that rejection is an immune response, and the recognition in the 1950s that the response is mounted by rapidly multiplying antigen-specific immune competent leukocytes (Fig. 3, top), prompted many experimental attempts to weaken the host versus graft immune reaction. This was done most frequently by administering total body irradiation before or after skin or organ transplantation. As late as 1960, however, these efforts had not produced a single example in animals of a long-surviving organ recipient.

BILLINGHAM, BRENT, AND MEDAWAR

The only potential ray of hope for clinical transplantation was contained in a three and a half page report published in the 3 October 1953 issue of the journal *Nature* (13). The first author was Rupert

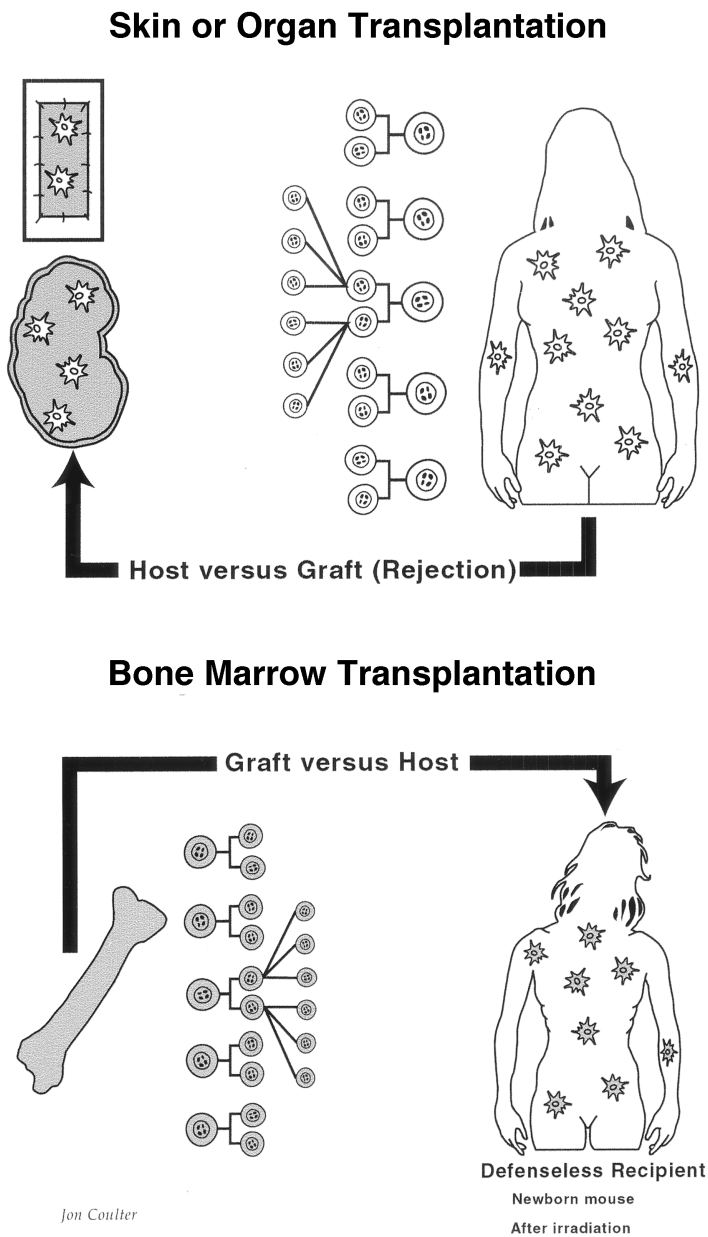


FIGURE 3. The historical view of the immune response induced by transplantation. Top: a unidirectional host versus graft response, here against a kidney on the left or above it a skin graft. Bottom: a mirror image of the top panel following bone marrow cell engraftment. Here, the recipient was rejected by an ostensibly unidirectional graft versus host response as the graft cells completely replaced the recipient immune system. The revised current concept is shown in Figure 14.

Billingham, one of the speakers at the Rhoads symposium of 1970. The other two were Leslie Brent and the team leader, the wartime investigator, Peter Medawar, who by now had reached the ripe old age of thirty-four. The trio soon would become known as the “holy trinity” of transplantation immunology.

What they had done was to inject leukocytes that had been isolated from the spleen or bone marrow of adult mice into the blood stream of newborn mouse recipients (Fig. 4, top). Because the immune system of the newborn mice was not yet developed enough to reject the donor leukocytes, these donor cells proliferated and appeared to have replaced the recipient immune cells (Fig. 4, bottom). This condition is known as *complete donor leukocyte chimerism*.

By 1955, comparable donor leukocyte chimerism was produced in adult mouse recipients whose immunity had been weakened by total

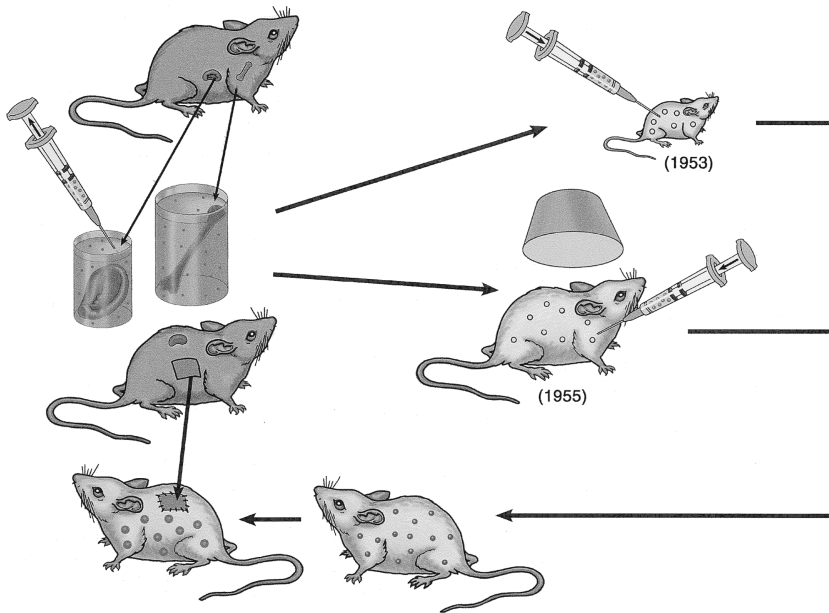


FIGURE 4. The mouse models of acquired tolerance described between 1953 and 1956. White cells (leukocytes) were isolated from the spleen or bone marrow of adult donor mice (upper left), and injected into the bloodstream of newborn mice (upper right), or of irradiated adult mice (mid-right). Under both circumstances, the recipient immune system was too weak to reject the foreign cells (dark shaded). With engraftment of the injected cells (i.e., donor leukocyte chimerism), the recipient mice now could freely accept tissues and organs from the leukocyte donor, but from no other donor (bottom left). Clinicians interested in organ transplantation promptly envisioned the use of bone marrow cell transplantation as a preparatory step to organ transplantation (see text).



FIGURE 5. Lethal graft versus host disease in which the engrafted immune cells of the donor attack and destroy the skin, lungs, intestine, liver, and other recipient tissues and organs. This complication in a recipient whose immune system is excessively weakened can be avoided only by donor-recipient tissue matching.

body irradiation (Fig. 4). Both the newborn and the irradiated adult chimeric recipients now could accept skin or other tissues from the original leukocyte donor, but from no other donor. These were the first examples of acquired donor-specific transplantation tolerance (Fig. 4).

The next step appeared to be obvious: i.e., the engraftment of bone marrow cells from the donor before or at the same time as organ transplantation. These plans ground to an abrupt halt when Medawar's associates, Billingham and Brent, discovered that the engrafted donor immune cells could turn the tables and reject the mouse recipients (14). In this truly horrible complication, called graft versus host disease, the recipient was eaten alive by the engrafted donor cells (Fig. 5). The "out of control" graft versus host response came to be widely viewed as a unidirectional immune reaction (Fig. 3, bottom) that was in essence a mirror image of the ostensibly one-way host versus graft reaction responsible for tissue and organ rejection (Fig. 3, top).

HUMAN BONE MARROW TRANSPLANTATION: 1968

Graft versus host disease was found to be avoidable in mice if the donor and recipient had a good tissue match. This condition could be met in inbred rodent models by using donors and recipients of selected strains. Clinical bone marrow transplantation was forestalled, however, until enough human tissue antigens were identified to permit the obligatory matching (Fig. 6, right) (9). By this time (1968), bone marrow cell engraftment was no longer a means to the end of organ transplantation. Instead, it became the definitive treatment for immune deficiency diseases, blood disorders, and numerous other indications.

THE EMPIRICAL DEVELOPMENT OF KIDNEY
TRANSPLANTATION: 1959–62

The escalation of mouse research to human application (Fig. 6, right) was heralded as a prime example of “bench to bedside” research. In contrast, kidney engraftment was accomplished first in humans rather than in animals (Fig. 6, left). Defined as patient and graft survival of at least one year, successes were recorded between January 1959 and the end of 1962 in the seven kidney recipients summarized in Table 2.

The first six patients were preconditioned with the irradiation strategy that had *never* worked in animals. The seventh was treated instead with daily post-transplant doses of an experimental drug called azathioprine (better known as Imuran®). The pathfinding first and seventh recipients were patients of Joseph Murray at the Peter Bent Brigham Hospital in Boston (6, 17), while the intervening five were treated at separate (competing) Paris hospitals (Table 2) (15, 16).

THE EPISTEMOLOGIC COLLAPSE

Although kidney transplant successes constituted a “breakthrough,” the results were utterly inexplicable. They had been achieved without

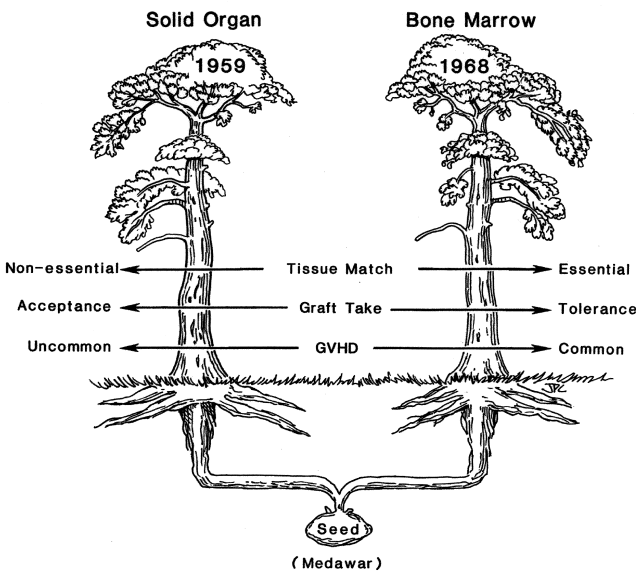


FIGURE 6. The divergence of the ostensibly unrelated fields of organ (left) and bone marrow transplantation. The conclusion that the two kinds of transplantation involved different mechanisms of engraftment was the basis for an epistemologic collapse in transplantation immunology (see text).

TABLE 2. Kidney transplantation ≥ 6 months survival as of March 1963

<i>Patient</i>	<i>City (Ref)</i>	<i>Date</i>	<i>Donor</i>	<i>Survival (mos.)</i>
1	Boston (6)	1/24/59	Fraternal twin	>50
2	Paris (15)	6/29/59	Fraternal twin	>45
3	Paris (16)	6/22/60	Unrelated	18 (Died)
4	Paris (15)	12/19/60	Mother	>12 (Died)
5	Paris (16)	3/12/61	Unrelated	18 (Died)
6	Paris (15)	2/12/62	Cousin	>13
7	Boston (17)	4/5/62	Unrelated	11

Boston: Joseph E. Murray (patients 1 and 7).
 Paris: Jean Hamburger (patients 2, 4, and 6), R. Küss (patients 3 and 5).

tissue matching, and with no hint of graft versus host disease (Fig. 6, left). Because none of the patients had been given a bone marrow cell infusion, it was universally concluded that organ engraftment involved mechanisms other than the donor leukocyte chimerism-associated ones of acquired tolerance. In effect, this assumption detached organ transplantation from the scientific base that had been established by the mouse tolerance discoveries of Billingham, Brent, and Medawar. With the agreement of both Murray (18) and Medawar (19), the consensus conclusion hardened into dogma and was not challenged for the next three decades.

Medawar remained puzzled by the success of organ transplantation for the rest of his life. Commenting on the search for unique mechanisms of organ engraftment and for strategies of “immunoregulation” with which to acquire tolerance, he concluded that “the spectacle of a scientist locked in combat with the forces of ignorance is not an inspiring one if, in the outcome, the scientist is routed” (20). In fact, the search for mechanisms of engraftment that were not associated with donor leukocyte chimerism lasted for forty years, and still goes on in many, if not most, transplant immunology laboratories.

KIDNEY INDUCED TOLERANCE?

Although the seven kidney cases that led to the divorce of organ and bone marrow transplantation were viewed as a collective triumph, they were, in fact, isolated exceptions to the usual outcome of failure. Two further findings in 1962 and 1963 in Denver now allowed kidney transplantation to be elevated from an uncertain experiment to a semi-reproducible, albeit still flawed, clinical service (21). These observations also marked the beginning of a trail that eventually would come back full cycle to the holy trinity of Billingham, Brent, and Medawar.

The first finding was that kidney graft rejection that occurred despite treatment with azathioprine could be readily reversed with large doses of adrenal cortical steroids, contravening the previous view that this immune response was one of biology's most inexorable reactions. The second observation was that organ grafts could self-induce tolerance. Tolerance was inferred from the rapid decline in many patients of the amount of treatment required at the outset to prevent or control rejection (Fig. 7). Such kidney recipients could have stable graft function while retaining a surprisingly complete ability to mount an immune defense against infections. Consequently, the patients were able to leave the protective "bubble" of quarantined hospital rooms, and return to an unrestricted environment.

The term "tolerance" to describe this privileged state was strongly criticized at the time. However, it proved to be the *bon mot*. Nine patients treated in Denver during 1962–63 had function of their kidney grafts for the ensuing four decades. Seven of the nine eventually stopped all immune suppression and remained drug-free for the periods shown in Figure 8 by the shaded portion of the horizontal bars (as long as thirty-eight years). One of the patients was murdered in a love triangle after thirty-six years of drug freedom, and had a normal kidney at autopsy. The remaining eight are the longest surviving kidney recipients in the world, all but one with normal kidney function (22).

The current world's champion was thirty-eight years old when he received a kidney from his younger sister. Eight years later, his photo-

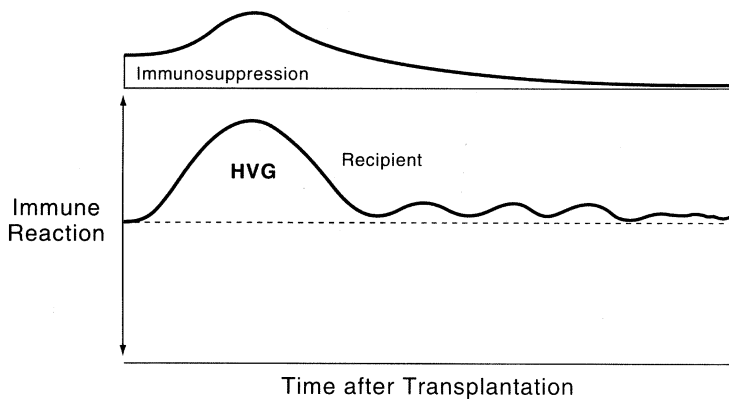


FIGURE 7. Two empirical observations in 1962–63 that made organ transplantation clinically practical. First, rejection is a highly reversible immune response, rather than being inexorable as previously thought. Second, the amount of immunosuppression necessary to maintain an allograft relative to that required at the outset frequently diminishes with time. This was attributed to "organ-induced tolerance," a conclusion that was highly controversial for many years.

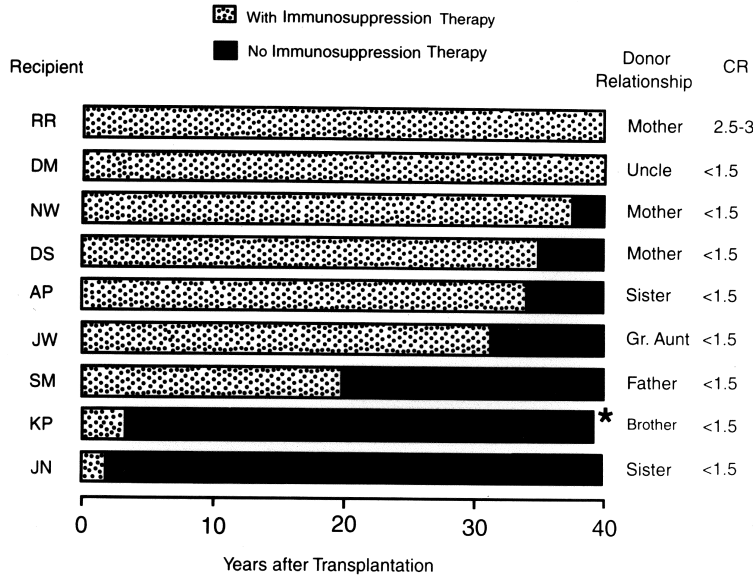


FIGURE 8. Current status of nine (19 percent) of the forty-six live donor kidney recipients treated at the University of Colorado over an eighteen-month period beginning in the autumn of 1962. The shaded portion of the horizontal bars depicts the time off immunosuppression. Four decades later, kidney function was normal in all but one of the nine patients. CR = serum creatinine (a measure of kidney function). *Murdered: kidney graft normal at autopsy. From ref. 22, by permission of the *Journal of the American College of Surgeons* 2002;195:587–610.

graph was projected at the 1970 Rhoads symposium (Fig. 9, upper). Now, almost eighty years old (Fig. 9, lower), he still has completely normal kidney graft function, and has been off all antirejection medication for more than a dozen years.

THE PRACTICAL TRIUMPH OF ORGAN TRANSPLANTATION

The treatment strategy developed by trial and error for kidney recipients proved to be generalizable for the transplantation of other organs. In July 1967, the first successes with liver transplantation were obtained in Denver (7) under immunosuppression with azathioprine and prednisone, to which a third agent, antilymphocyte globulin (ALG) was added (23). Differing from the pioneer kidney recipients only in their much greater numbers, many of the early liver recipients were able to stop their antirejection drugs (24). Now, after more than a third of a century, the woman shown in Figure 10 is the longest surviving liver recipient in the world.

By the early 1970s, the feasibility of transplantation of the liver,

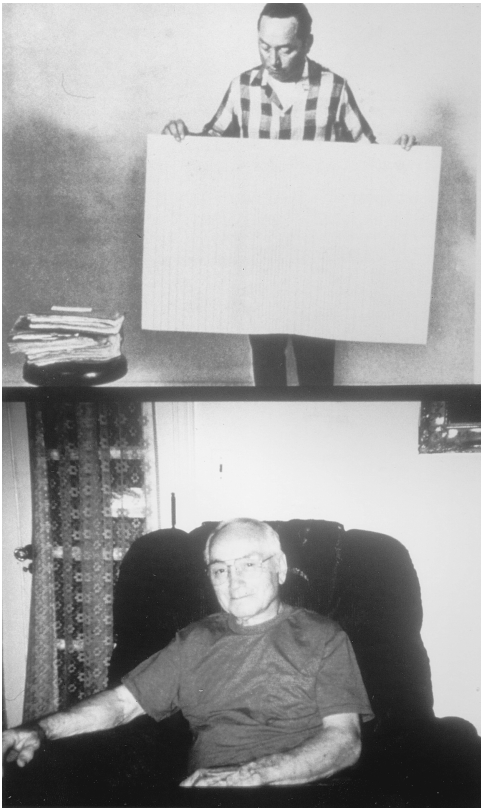


FIGURE 9. The world's longest surviving recipient of a kidney allograft. Top: slide projected at the Rhoads symposium of 1970, almost eight years after transplantation. Bottom: recent photograph a third of a century later.



FIGURE 10. The world's longest surviving liver recipient with her husband, a third of a century after transplantation at the age of three

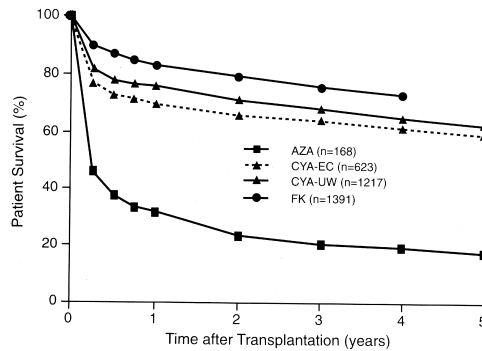


FIGURE 11. Stepwise improvements in patient survival after liver replacement. These were associated with the advent of increasingly potent immunosuppressive drugs. AZA = azathioprine; CYA = cyclosporine; FK = tacrolimus.

heart, and pancreas had been established unequivocally. The death rate and morbidity remained so high, however, even with cadaver kidney transplantation, that the future seemed truly bright only for live donor renal transplantation from blood relatives. A frustrating decade passed before more potent drugs became available to replace azathioprine: cyclosporine in 1979–80 (25, 26) and tacrolimus in 1989–90 (27).

Then, it was possible for the first time to represent transplantation of the liver (Fig. 11) (28, 29) and other cadaveric organs as a reasonably predictable service. By the end of the twentieth century, transplantation of all of the vital organs had become part of the medical armamentarium in almost every developed country in the world.

But the triumph was bittersweet. The daily antirejection treatment continued to pose risks from infections and from malignant tumors that are normally kept under control by the immune system. In addition, none of the drugs was free of toxic side effects, some of which could ruin the transplanted organs they were designed to protect. There were other concerns. It had been anticipated that reduction of the incidence of acute rejection to near zero would result in a larger number of drug-free patients such as those that had been seen in the pioneer era. But tolerant recipients were almost never seen again. In addition, chronic rejection now emerged as the most intractable problem in transplantation.

AN EPIPHANY

It was obvious that further progress in transplantation would require elucidation of the enigmatic mechanisms of both organ and bone

marrow cell engraftment, rather than the development of ever more potent immunosuppression. Was it possible, as I had suspected since the 1960s (30), that successful organ and bone marrow transplantation were merely variations on the same theme? If so, organ engraftment was by definition a state of partial tolerance, and there should be surviving donor leukocytes in the tissues or blood of the successfully treated organ recipient.

What could be the source of the donor cells? It had long been known that the “passenger leukocytes” of bone marrow origin (Fig. 2, left) disappear from successfully transplanted organs (Fig. 2, right). It had been thought that these cells were selectively destroyed by the host immune response with selective preservation of the organs’ specialized cells (e.g., those that excrete urine). Instead, we now postulated that the passenger leukocytes migrated into the recipient, and that organ transplantation could, in fact, be the unrecognized equivalent of a small bone marrow cell infusion. To test this hypothesis, bits of tissue were obtained in 1992 from various locations in recipients who had borne functioning kidney, liver, and other kinds of organ grafts for as long as thirty years (in Fig. 12, a liver).

With microscopic studies and with corroborating DNA analyses, the presence of small numbers of the donor cells was demonstrated in

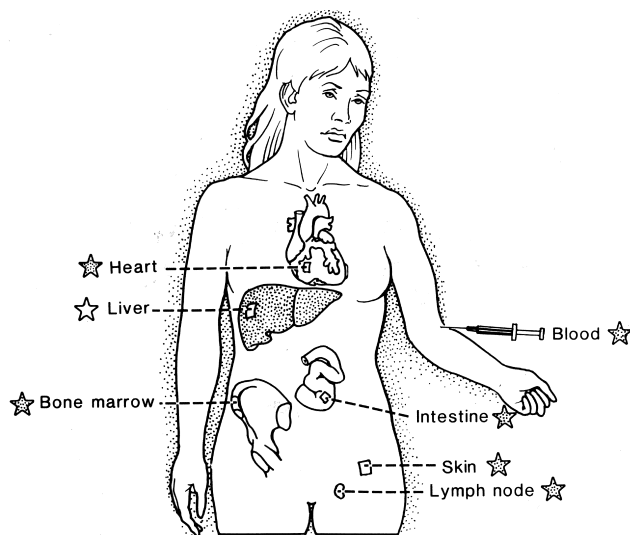


FIGURE 12. Host sites sampled in studies in 1992 of the longest surviving kidney and liver recipients in the world. Donor leukocytes were looked for in host blood, skin, and lymph nodes as well as in the allograft (here liver) of all patients, and in selected cases, biopsies also were taken from the heart, intestine, other organs, or bone marrow. The concepts depicted in Figures 13 and 14 were deduced from the finding of low-level donor leukocyte chimerism in all patients, and confirmed in a series of controlled animal experiments.

all organ recipients studied (24, 31). A grand design could now be pieced together, whose very simplicity had cloaked its existence and delayed its discovery. Rather than resulting from a one-way immune reaction (Fig. 3, top), the outcome after organ transplantation, whether rejection or engraftment, was the product of two immune responses that begin within minutes after organ transplantation as myriads of the passenger leukocytes begin to leave the graft for peripheral locations in the patient (Fig. 13).

The resulting confrontation of the donor and recipient immune cells was a classical David versus Goliath mismatch, in which the role of David was played by the less numerous leukocytes of the organ. In addition to inducing an attack from the recipient immune system (the Goliath), these donor leukocytes mounted a counterattack (i.e., a graft versus host response). The responses, each to the other, of the aroused and multiplying donor and recipient leukocytes (Fig. 14, upper) could result in their mutual exhaustion and disappearance. The technical term for the process is “reciprocal clonal exhaustion-deletion.”

Reciprocal clonal exhaustion-deletion was, in fact, the seminal mechanism of organ engraftment and of acquired tolerance. Although outnumbered many times by the leukocytes of the recipient immune system, residual donor cells could escape destruction by migrating to inaccessible areas in the recipient body, where they were sheltered from

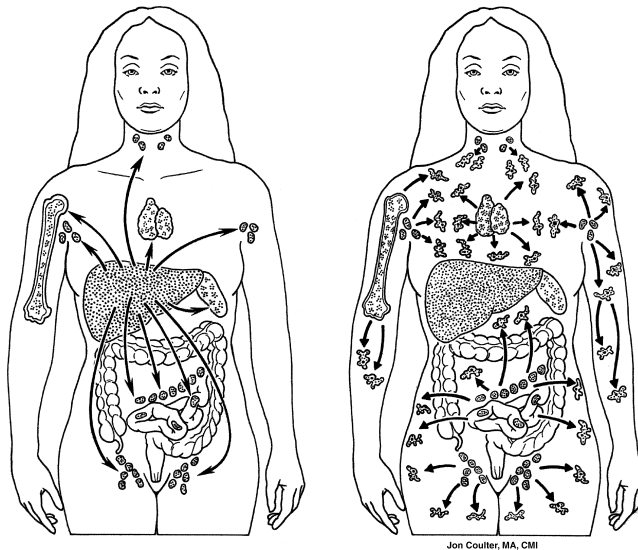


FIGURE 13. Initial preferential migration of passenger leukocytes from organ allografts (here a liver) to host lymphoid organs (left), where they induce a donor-specific immune response. After about thirty days, many of the surviving cells move on to non-lymphoid sites (right).

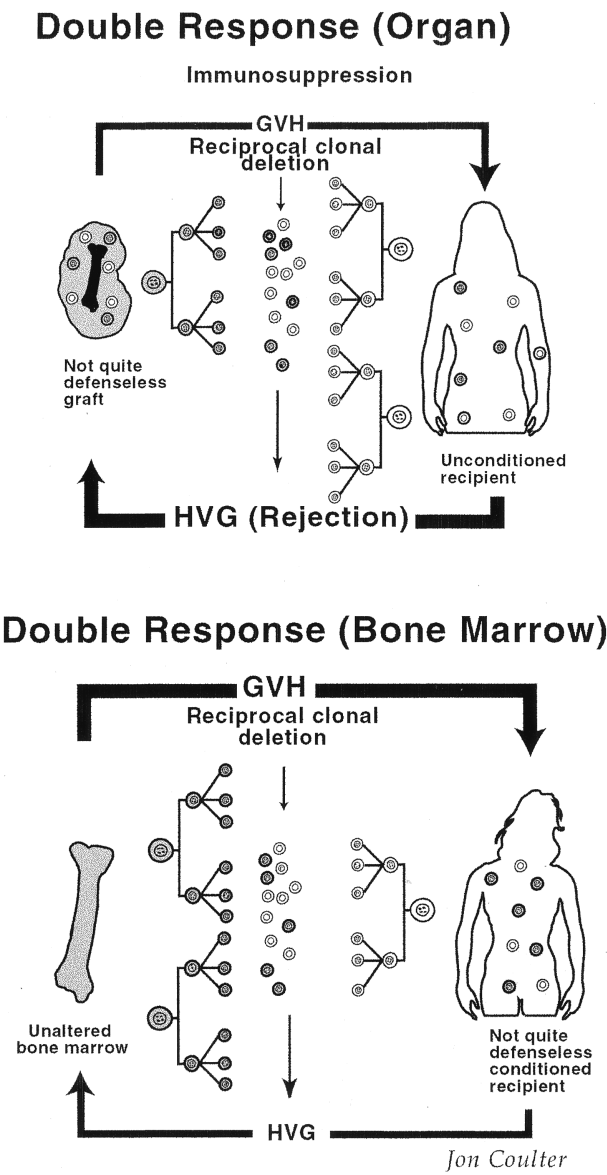


FIGURE 14. Current definition of allograft acceptance in terms of double and mutually canceling immune reactions (compare with the historical view shown in Fig. 3). The dominant reaction usually is host versus graft (HVG) after organ transplantation (top), and most commonly graft versus host (GVH) after bone marrow transplantation (bottom). After both kinds of transplantation, however, the effective opposition to and modulation of the stronger responses by the minority cell population are the key to engraftment.

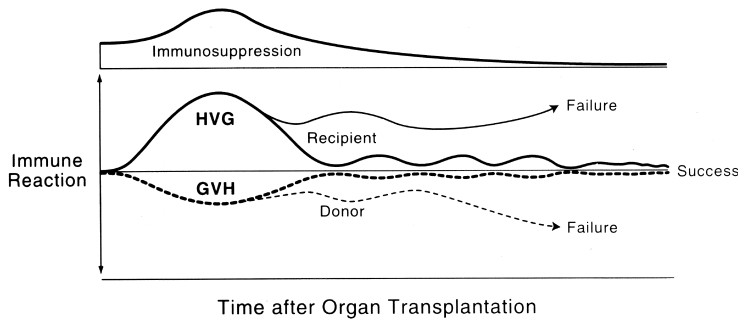


FIGURE 15. Contemporaneous HVG (upright curves) and GVH (inverted curves) responses following transplantation. In contrast to the usually dominant HVG reaction of organ transplantation, the GVH reaction usually is dominant after bone marrow cell transplantation to the irradiated or otherwise immunodepressed recipient. Therapeutic failure with either type of transplantation implies the inability to control one, the other, or both of the contemporaneous responses with a protective umbrella of immunosuppression. From ref. 33, by permission of the *New England Journal of Medicine* 1998;339:1905–13.

immune injury. From these privileged locations, the residual donor cells may return to the main circulation and sustain the clonal exhaustion-deletion induced at the outset (32, 33).

In the mirror-image scenario, successful bone marrow transplantation did *not* imply complete replacement of the cellular immune system as had previously been thought (Fig. 3, lower). A small residual population of recipient immune cells could always be found in bone marrow recipients who ostensibly had complete donor leukocyte chimerism (Fig. 14, lower) (34). The double immune reaction common to both organ and bone marrow transplantation differed primarily in the relative magnitude of the host versus graft (the rejection) response (upright curves in Fig. 15) and the graft versus host response (the inverted curves).

THE FACILITATION OF TOLERANCE MECHANISMS

In most organ centers today, heavy multidrug immunosuppression is begun at the time of transplantation, and decreased to maintenance levels over many succeeding weeks or months. The objective has been to reduce the antigraft immune response as much as possible, with the assumption that this will minimize early graft loss and ultimately result in a better long-term course. Now, we realized that the immune response that led to rejection was also the first stage in the development of tolerance, and that this could be inadvertently undermined by the standard policy of heavy early post-transplant immunosuppression.



FIGURE 16. Rolf Zinkernagel (1944–). Swiss physician-immunologist whose discovery (with Peter Doherty) of the mechanisms of the adaptive immune response to non-cytopathic microorganisms earned the Nobel Prize in 1996. The collaboration with Zinkernagel between 1997 and 2001 placed the immunology of transplantation, infection, oncology, and self/non-self discrimination on common ground (33), and resulted in the development of better treatment strategies for transplant recipients (35).

In collaboration with Rolf Zinkernagel of Zurich (Fig. 16), an alternative strategy was developed, the purpose of which was to lower the donor-specific immune response into a more deletable range (35). This involved two stages. First, the cellular immune response of the recipient was weakened in advance of transplantation by the administration of antilymphocyte globulin (the pretreatment principle). The enfeebled immune response was then further reduced after transplantation with just enough antirejection treatment to prevent irreversible destructive immunity, but not so much that the processes of immune activation and exhaustion-deletion were eliminated (the principle of minimal post-transplant immunosuppression).

These simple therapeutic principles were then applied in nearly

seven hundred cases of kidney, liver, intestine, pancreas, and lung transplantation. The first eighty-two of these patients were reported in the 3 May 2003 issue of the journal *Lancet* (36). The most important conclusion was that major improvements in transplantation are readily achievable with this strategy, including relief of recipients from much of the burden of chronic antirejection therapy.

XENOTRANSPLANTATION

The same treatment principles are expected to apply for the transplantation of animal organs into humans (xenotransplantation). In July 2002, cloned transgenic pigs were produced in which the principal gene that has precluded xenotransplantation was deleted (37). These unique animals are ready to have their organs tested by transplantation to non-human primates.

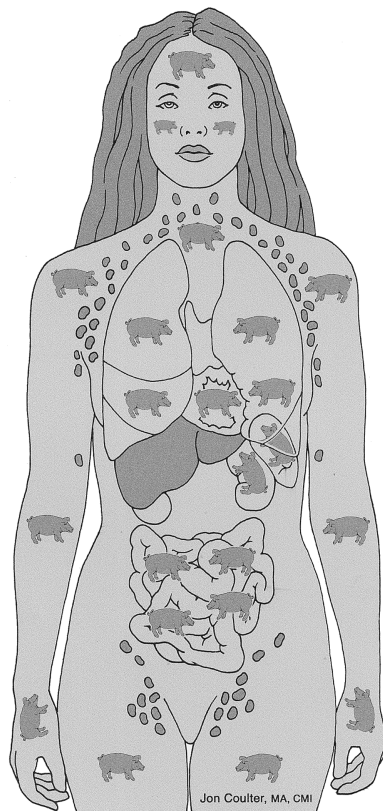


FIGURE 17. Disseminated pig leukocytes throughout the body of a human recipient of a porcine liver xenograft. This outcome is expected if transgenic pig organs are successfully transplanted to humans (see text).

It is virtually certain that more genetic modifications will be needed. But it is equally clear that when xenotransplantation comes to the clinic, the mechanisms and rules of xenoengraftment will be the same as those of human-to-human transplantation. The crucial migratory cells that are at the heart of engraftment and acquired tolerance will, of course, be those of the pig (Fig. 17).

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